COLUMBIA
RESEARCH
LABORATORIES, INC.

June 1, 1999

VIA FACSIMILE (301) 827-6870
AND U.S. MAIL

Docket Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket No. 98N-1265
Federal/State Memorandum of Understanding on
Interstate Distribution of Compounded Drug Products

Dear Sir or Madam:

As a manufacturer of prescription and over-the-counter pharmaceuticals, Columbia Laboratories has a keen interest in appropriate federal and state regulation of compounded drug products. In particular, Columbia is concerned by the large-scale compounding and interstate distribution of hormone replacement therapies, many of which we believe to be essentially copies of commercially available drug products. Our concern is based on the threat to the public health from products made without appropriate controls and testing, as well as the unfair competitive advantage that is conveyed upon pharmacies that are manufacturing drug products without having to meet regulatory requirements, such as conformance to GMPs, that are imposed on traditional manufacturers.[1] For that reason, we are heartened by enactment of § 503A of the Federal Food, Drug, and Cosmetic Act (the Act), which contains provisions that, together, "limit[] the scope of compounding so as to prevent manufacturing under the guise of compounding." H. Rpt. 105-399, Conference Report to S. 830, Food and Drug Administration Act of 1997 (FDAMA), at 94.

A key component is § 503A(b)(3)(B), which provides for development of a standard FDA-state memorandum of understanding (MOU) that (among other things) "addresses the distribution of inordinate amounts of [compounded] drug products interstate," and limits a pharmacy or physician's interstate distribution to five percent of total orders if the compounding takes place in a state that has not entered into the MOU. The December 23, 1998 draft MOU that FDA has issued for comment represents an important step toward implementing the restrictions that are the heart of § 503A; Columbia is submitting these comments to suggest several ways to enhance the effectiveness of the MOU in achieving that goal.

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1. The septicemia experienced by two patients who were administered pharmacy compounded riboflavin injections, and which led to the Denver District Office's April 7, 1999 warning letter to College Pharmacy, is an example of the very real risks posed by pharmacy compounding.

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The FDAMA conference report expresses congressional intent that the MOU "provide guidance on the meaning of inordinate amounts, including any circumstances under which the compounding of drug products for interstate shipment in excess of 5 percent of total prescription orders would . . . not be deemed inordinate." *Id.*, at 95. Under the terms of the draft MOU, however, a pharmacy or physician is considered to distribute interstate an inordinate amount of compounded drugs if annually (1) the number of compounded prescriptions dispensed or distributed interstate equals or exceeds 20% of all prescriptions dispensed or distributed by that pharmacy or physician, or (2) any one compounded drug product accounts for more than 5% of the total number of prescriptions. Draft MOU § III.C.1. The 20% threshold is a clear departure from the 5% limit that Congress intended, yet neither the draft MOU nor the Federal Register notice announcing its availability explain why a different standard was chosen, or discuss the "circumstances under which" this higher limit is appropriate. In essence, the draft MOU turns the standard on its head, setting a general limit of 20% and defining special circumstances under which a 5% limit is imposed. Consistent with the express intent of Congress, Columbia believes the final MOU should state that the interstate shipment of compounded drug in excess of 5% of total prescriptions is considered inordinate.

Of course, whatever threshold is adopted must be enforced. In that regard, although Columbia appreciates that the MOU "reflects FDA's policy to defer to State and local officials for the regulation of the day-to-day practice of pharmacy," draft MOU § II.D, we are concerned about the adequacy of state obligations to take regulatory action or inform FDA. This is particularly important in light of the fact that the draft MOU gives states the leading role in investigating compounding activities and identifying violations of federal law.

Under the MOU as currently drafted, if a state board of pharmacy concludes that a pharmacy's interstate distribution of compounded drug products exceeds 20% of total prescriptions, the state's only obligation under § III.C.1 is to "take action," which ***may*** but does not necessarily include "State regulatory action, referral to FDA for action, or joint State-FDA action." Although FDA explicitly retains its authority under the FDCA, draft MOU § III.E, that authority can be exercised meaningfully only if the agency is aware of violative activities in a timely manner. The draft MOU would require a state to forward to FDA information about any "significant violation" of the 20% limit, but it does not define what constitutes a "significant violation," sets no time frame within which FDA must be notified, and apparently contemplates FDA action only after state investigation and if the state subsequently asks FDA to take action. Draft MOU § III.D.3. Moreover, there is the very real possibility that, as a practical matter, states

would not be able to effectively investigate complaints or allegations that a pharmacy is violating the 20% limit. Although the draft MOU requires signatory state agencies to affirm that they have the authority and resources to meet their obligations under the MOU, draft MOU § III.A, the meaning of that general affirmation is far from clear. For example, does having adequate authority include subpoena power, or the right to inspect facilities and records? Even if it does, are pharmacies required to keep the types of records necessary for an investigator to be able to ascertain what percentage of prescriptions consist of interstate distribution of compounded drug products?

Accordingly, Columbia urges FDA to revise the draft MOU, to (1) require states to take action to curtail interstate distribution of inordinate amounts of compounded drug products, (2) require notification to FDA of all violations, not just those that might be deemed "significant," (3) set explicit, short time frames within which states must investigate possible violations and notify FDA, (4) make clear that FDA need not await a referral or request for action by the state, and (5) identify more specifically the authority and resources state agencies must posses to be able to meet their obligations under the MOU.

Sincerely,

Howard L. Levine/pk

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